

1. A method of constructing a library of phenotypic profiles of nematode worms which comprises the steps of:

2. A method as claimed in claim 1 wherein in step (c) at least three changed characteristics are scored.

- 15
3. A method as claimed in claim 1 or claim 2 wherein in step (c) at least six changed characteristics are scored.

4. A method as claimed in any preceding claim wherein in step (c) at least
20 ten characteristics are scored.

5. A method as claimed in any preceding claim wherein said worm is *Caenorhabditis elegans*.

- 25 6. A method as claimed in any preceding claim wherein steps (a) to (c) are
carried out in respect of substantially every gene in the worm genome.

7. A method as claimed in any preceding claim which includes the step of manipulating said worm to generate said defect in said at least one gene.

8. A method as claimed in any preceding claim wherein said defect is selected from the absence of expression of said gene, the reduction in expression of said

gene, the over-expression of said gene, the expression of a functionally defective protein, the expression of a truncated protein, the misexpression of a protein, the ectopic misexpression of a protein, the expression of a protein of altered stability or the alteration of gene expression as a function of time.

5

9. A method as claimed in claim 7 or 8 wherein said manipulation is carried out on wild-type *C. elegans* or a selected mutant thereof.

10

10. A method as claimed in claim 9 wherein said selected mutant harbours multiple mutations.

11. A method as claimed in claim 7 or 8 wherein said manipulation is carried out on *C. elegans* carrying a reporter gene.

15

12. A method as claimed in claim 11 wherein said reporter gene is LacZ or green fluorescent protein (GFP).

20

13. A method as claimed in any one of claims 7 to 12 wherein said manipulation is carried out on a transgenic *C. elegans*.

14. A method as claimed in claim 13 wherein said transgenic *C. elegans* expresses a human gene.

25

15. A method as claimed in claim 14 wherein said human gene is a known drug target.

16. A method as claimed in claim 14 or claim 15 wherein said human gene is one associated with a human disease.

30

17. A method as claimed in claim 14 or 15 wherein said human gene is a candidate human disease gene.

18. A method as claimed in any of claims 7 to 17 wherein said manipulation

is carried out on only a sub-set of *C. elegans* cells.

19. A method as claimed in any preceding claim wherein changed characteristics in said worm carrying said defect compared to a worm that does not carry said defect are identified by light microscopy, differential interference contrast optics, fluorescence microscopy, immunochemical detection or spectrophotometric detection, radiation detection, calorimetric detection, fluorescence detection or luminescence detection.

20. A method as claimed in any preceding claim wherein changed characteristics in said worm carrying said defect compared to a worm that does not carry said defect are identified by a pH change or a change in electrical potential.

21. A method as claimed in any preceding claim wherein said plurality of changed characteristics are scored in a predetermined order to generate said phenotypic profile.

22. A method as claimed in any preceding claim wherein the scoring of said plurality of changed characteristics is repeated at predetermined intervals of time.

23. A method as claimed in any preceding claim wherein said phenotypic profiles are stored electronically.

24. A method as claimed in any preceding claim wherein at least one of said plurality of characteristics is selected from the list shown in Table 1.

25. A method as claimed in any one of the preceding claims wherein step (b) comprises measuring changes in two or more characteristics selected from the group consisting of: viability, life cycle, body shape, movement behaviour, mechanotransduction, pharynx pumping, defecation and fertility.

26. A method of constructing a library of phenotypic profiles of nematode worms which comprises the steps of:

0057473 034701
10/10/03 13:44:59

- (a) exposing a worm to a compound,
(b) measuring any changes in identifiable characteristics of said worm as a result of exposure to said compound,
(c) systematically scoring a plurality of any said changed characteristics to establish a phenotypic profile associated with said compound,
(d) simultaneously or sequentially repeating steps (a) to (c) in respect of each of a plurality of different compounds and
(e) collating the phenotypic profiles so obtained into a library of said profiles.

27. A method as claimed in claim 26 wherein in step (c) at least three changed characteristics are scored.

28. A method as claimed in claim 27 wherein in step (c) at least six changed characteristics are scored.

29. A method as claimed in claim 28 wherein in step(c) at least ten changed characteristics are scored.

30. A method as claimed in any one of claims 26 to 29 wherein said nematode worm is *C. elegans*.

31. A method as claimed in any one of claims 26 to 30 wherein each of said plurality of different compounds has a known pharmacological activity.

32. A method as claimed in any one of claims 26 to 30 wherein each of said plurality of different compounds is one which is known to interact with a particular biochemical pathway.

33. A method as claimed in any one of claims 26 to 30 wherein each of said plurality of different compounds has no known pharmacological activity or biochemical interaction.

34. A method as claimed in any one of claims 26 to 30 wherein each of said

09257478.081701

plurality of different compounds is from a combinatorial library.

35. A method as claimed in any one of claims 26 to 34 wherein said worm
to which said compound is exposed is wild-type *C. elegans* or a selected mutant
thereof.

36. A method as claimed in claim 35 wherein said selected mutant harbours
multiple mutations.

37. A method as claimed in any one of claims 26 to 34 wherein said worm
to which said compound is exposed is *C. elegans* carrying a reporter gene.

38. A method as claimed in claim 37 wherein said reporter gene is LacZ or
GFP.

39. A method as claimed in any one of claims 26 to 38 wherein said worm
to which said compound is exposed is a transgenic *C. elegans*.

40. A method as claimed in claim 39 wherein said transgenic *C. elegans*
expresses a human gene.

41. A method as claimed in claim 40 wherein said human gene is a known
drug target.

42. A method as claimed in claim 40 wherein said human gene is one
associated with a human disease.

43. A method as claimed in claim 40 wherein said human gene is a
candidate disease gene.

44. A method as claimed in any one of claims 30 to 43 wherein said worm is
exposed to said compound by feeding the worm on bacteria which have been exposed

to said compound.

45. A method as claimed in claim 44 wherein said bacteria are *E. coli*.

5 46. A method as claimed in any one of claims 26 to 45 wherein said compound is linked to another compound or carrier substance.

47. A method as claimed in anyone of claims 26 to 46 wherein any changed characteristics in said worm resulting from exposure to said compound are identified by
10 light microscopy, differential interference contrast optics, fluorescence microscopy, immunochemical detection, spectrophotometric detection, radiation detection, colorimetric detection, fluorescence detection or luminescence detection.

48. A method as claimed in any one of claims 26 to 47 wherein any changed
15 characteristics in said worm resulting from said compound are identified by a pH change or a change in electrical potential.

49. A method as claimed in any one of claims 26 to 48 wherein said
20 plurality of changed characteristics are scored in a predetermined order to generate said profile.

50. A method as claimed in any one of claims 26 to 49 wherein the scoring said plurality of changed characteristics is repeated at predetermined time intervals.

25 51. A method as claimed in any one of claims 26 to 50 wherein said scoring of changed characteristics is carried out using essentially the same scoring protocol as used in a method in accordance with any one of claims 1 to 25.

30 52. A method as claimed in any one of claims 26 to 51 which comprises the further step of storing the said phenotypic profiles electronically.

09857478.051701

53. A method as claimed in any one of claims 26 to 52 wherein at least one of said plurality of characteristics is selected from the list shown in Table 1.

54. A method as claimed in any one of claims 26 to 53 wherein step (b) comprises measuring changes in two or more characteristics selected from the group consisting of: viability, life cycle, body shape, movement behaviour, mechanotransduction, pharynx pumping, defecation and fertility.

55. A method of constructing a library of phenotypic profiles of nematode worms which comprises the steps of:

- (a) exposing a worm to an environmental change,
- (b) measuring any changes in identifiable characteristics as a result of said environmental change,
- (c) systematically scoring a plurality of any said changed characteristics to establish a characteristic phenotypic profile associated with said change,
- (d) simultaneously or sequentially repeating steps (a) to (c) for each of a plurality of different environmental changes and (e) collating the phenotypic profiles so obtained into a library of said profiles.

56. A method as claimed in claim 55 wherein in step (c) at least three changed characteristics are scored.

57. A method as claimed in claim 56 wherein in step (c) at least six changed characteristics are scored.

58. A method as claimed in claim 57 wherein in step (c) at least ten changed characteristics are scored.

59. A method as claimed in any of claims 55 to 58 wherein said environmental change is a change in the pH to which the worm is exposed and in step (d) each of the plurality of environmental changes comprises a different pH.

09557478.081701

60. A method as claimed in any one of claims 55 to 58 wherein said environmental change is a change in the osmolarity to which the worm is exposed and in step (d) each of the plurality of environmental changes comprises a different osmolarity.

61. A method as claimed in any one of claims 55 to 58 wherein said environmental change is a change in the temperature to which the worm is exposed and in step (d) each of the plurality of environmental changes comprises a change in temperature.

62. A method as claimed in any one of claims 55 to 58 wherein said environmental change comprises exposure to radiation and in step (d) each of said plurality of environmental changes comprises a different level of radiation.

63. A method as claimed in any one of claims 55 to 58 wherein said environmental change comprises exposure to a virus and in step (d) each of said plurality of environmental changes comprises exposure to a different virus.

64. A method as claimed in any one of claims 55 to 58 wherein said environmental change comprises exposure to a bacterium and in step (d) each of said plurality of environmental changes comprises exposure to a different bacterium.

65. A method as claimed in any one of claims 55 to 64 wherein said worm is *C. elegans*.

66. A method as claimed in any one of claims 55 to 65 including a further feature as defined in any one of claims 5 to 54.

67. A method as claimed in any one of claims 55 to 66 wherein said scoring of changed characteristics is carried out using essentially the same scoring protocol as used in a method in accordance with claims 1 to 54.

68. A method as claimed in any one of claims 55 to 67 wherein step (b)

00857473 081701

comprises measuring changes in two or more characteristics selected from the group consisting of: viability, life cycle, body shape, movement behaviour, mechanotransduction, pharynx pumping, defecation and fertility.

5 69. A method of constructing a multiple library of phenotypic profiles of nematode worms which method comprises carrying out all of the methods of claims 1, 26 and 55.

10 70. A method as claimed in claim 69 wherein step (b) of the method of at least one of claims 1, 26 and 55 comprises measuring changes in two or more characteristics selected from the group consisting of: viability, life cycle, body shape, movement behaviour, mechanotransduction, pharynx pumping, defecation and fertility.

15 71. A method of determining the mode of action of a compound which method comprises the steps of;
 (a) exposing a nematode worm to said compound
 (b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound,
 (c) systematically scoring a plurality of changed characteristics to establish a
20 phenotypic profile associated with said compound and
 (d) comparing said phenotypic profile with a library of reference phenotypic profiles wherein said library of reference profiles is obtainable by carrying a method in accordance with any of claims 1 to 70.

25 72. A method of determining whether a compound or combination of compounds interacts with a particular gene or biochemical pathway which method comprises the steps of;
 (a) exposing a nematode worm to said compound or combination of compounds
 (b) measuring any changes in identifiable characteristics of said worm as a
30 result of said exposure,
 (c) systematically scoring a plurality of any changed characteristics to establish a phenotypic profile associated with said compound or combination of compounds, and

09557478.001701

73. A method of finding an alternative treatment for a human disease which method comprises the steps of:

- 10 (c) systematically scoring a plurality of any changed characteristics to establish
a phenotypic profile for said compound and

74. A method of finding a biochemical pathway in which a compound known to have pharmacological activity acts which method comprises the steps of:

- (a) exposing a nematode worm to the known compound,
(b) measuring any changes in the identifiable characteristics of said worm as a
20 result of exposure to said compound,

(c) systematically scoring a plurality of any changed characteristics to establish a phenotypic profile for said compound, and

(d) comparing said profile with a library of reference profiles, said library of reference profiles being obtainable by carrying out a method in accordance with claim 25 32.

75. A method of finding a potential new medicinal indication for a compound of known pharmaceutical activity which method comprises the steps of:

- 30 (a) exposing a nematode worm to the known compound,
(b) measuring any changes in the identifiable
characteristics of said worm as a result of exposure to said compound,
(c) systematically scoring a plurality of any

changed characteristics to establish a phenotypic profile for said compound and

(d) comparing said profile with a library of reference profiles, said library of reference profiles being obtainable by carrying out a method in accordance with any one of claims 1 to 70.

76. A method as claimed in claim 75 wherein said library of reference profiles is obtainable by carrying out a method in accordance with any one of claims 24 to 26.

77. A method of identifying the mechanism of action of any side effects associated with a compound of known pharmaceutical activity which method comprises the steps of;

- (a) exposing a nematode worm to the known compound,
- (b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound,
- (c) systematically scoring a plurality of any changed characteristics to establish a phenotypic profile for said compound and
- (d) comparing said profile with a library of reference profiles, said library of reference profiles being obtainable by carrying out a method in accordance with claim 32 and/or any of claims 1 to 25.

78. A method of attributing a particular gene to a particular biochemical pathway in *C. elegans* which method comprises the steps of:

- (a) exposing a nematode worm to a compound known to operate in a particular biochemical pathway,
- (b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound
- (c) systematically scoring a plurality of any changed characteristics to establish a phenotypic profile for said compound, and
- (d) comparing said, profile with a library of reference phenotypic profiles said library of reference profiles being obtainable by carrying out a method in accordance

with any one of claims 1 to 25.

79. A method as claimed in any of claims 71 to 78 wherein said nematode worm is selected from wildtype *C. elegans*, a mutant *C. elegans* comprising one or more mutations, a *C. elegans* carrying a reporter gene or a transgenic *C. elegans*.

80. A method as claimed in claim 79 wherein said transgenic *C. elegans* expresses a human gene.

81. A method as claimed in any one of claims 71 to 80 wherein step (b) comprises measuring changes in two or more characteristics selected from the group consisting of: viability, life cycle, body shape, movement behaviour, mechanotransduction, pharynx pumping, defecation and fertility.

82. A method for elucidating biochemical pathways in a nematode worm which method comprises the steps of:

- (a) generating a defect in at least one gene in said worm,
- (b) measuring any changes in identifiable characteristics of said worm compared to a worm without said defect,
- (c) systematically scoring a plurality of any said changed characteristics to establish a phenotypic profile for said defect, and
- (d) comparing said profile with a library of reference phenotypic profiles, said library of references profiles being obtainable by carrying out a method in accordance with any one of claims 1 to 25

83. A method as claimed in claim 82 wherein said nematode worm is selected from wild-type *C. elegans*, a mutant *C. elegans* comprising one or more mutations, a *C. elegans* carrying a reporter gene or a transgenic *C. elegans*.

84. A method as claimed in claim 82 wherein said defect is selected from the absence of expression of said gene, the reduction in expression of said gene, the expression of a functionally defective protein, the expression of a truncated protein, the misexpression of a protein, the ectopic misexpression of a protein, the expression of a

protein of altered stability or the alteration of gene expression as a function of time.

85. A method as claimed in any one of claims 82 to 84 wherein at least three, preferably at least six
5 and more preferably at least ten changed characteristics are scored.

86. A method as claimed in any of claims 82 to 85 which includes the features described in any one of claims 19 to 25.

10 87. A method of constructing a library of nematode worms which method comprises the steps of:

(a) providing a worm having a defect in at least one gene.

(b) measuring any changes in identifiable characteristics of said worm compared to a worm without said defect,

15 (c) systematically scoring a plurality of any said changed characteristics to establish a characteristic phenotypic profile associated with said defect,

(d) simultaneously or sequentially repeating steps (a) to (c) in respect of each of a plurality of worms, and

20 (e) producing a library of said worms each identifiable by their phenotypic profiles.

88. A method as claimed in claim 87 wherein said phenotypic profiles are collated into a library.

25 89. A method as claimed in claim 87 and 88 comprising any one of the features described in any one of claims 2 to 25.

90. A method of constructing a library of nematode worms which method comprises the steps of:

30 (a) exposing a worm to a compound,

(b) measuring any changes in identifiable characteristics of said worm as a result of exposure to said compound,

00357473.081701

(c) systemically scoring a plurality of any said changed characteristics to establish a phenotypic profile associated with said compound,

(d) simultaneously or sequentially repeating steps (a) to (c) in respect of each of a plurality of different compounds, and producing a library of said worms each identifiable by their phenotypic profiles.

91. A method as claimed in claim 90 wherein said phenotypic profiles are collated into a library.

92. A method as claimed in claim 90 or 91 comprising any one of the features disclosed in any one of claims 27 to 54.

93. A method of constructing a library of nematode worms which method comprises the steps of:

(a) exposing a worm to an environmental change,
(b) measuring any changes in identifiable characteristics as a result of said environmental change,

(c) systematically scoring a plurality of any said changed characteristics to establish a characteristic phenotypic profile associated with said change,

(d) simultaneously or sequentially repeating steps (a) to (c) in respect of each of a plurality of different environmental changes, and

(e) producing a library of said worms each identifiable by their phenotypic profile.

94. A method as claimed in claim 93 wherein said phenotypic profiles are collated into a library.

95. A method as claimed in claim 93 or claim 94 comprising any one of the features disclosed in any one of claims 56 to 70.

96. A method of determining the mode of action of a compound which method comprises the step of:

09557478.081704
102780.82425560

- (a) exposing a nematode worm to said compound,
- (b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound,
- (c) systematically scoring a plurality of any said changed characteristics to establish a phenotypic profile associated with said compounds, and
- (d) comparing said phenotypic profile with the library of phenotypic profiles obtainable by the method of any one of claims 88, 91 or 94.

97. A method of determining whether a compound or a combination of compounds interacts with a particular gene or biochemical pathway which method comprises the steps of:

- (a) exposing an nematode worm to said compound or combination of compounds,
- (b) measuring any changes in identifiable characteristics of said worm as a result of said exposure,
- (c) systematically scoring a plurality of any said changed characteristics to establish a phenotypic profile associated with said compounds or combination of compounds, and
- (d) comparing said phenotypic profile with a library of reference profiles wherein said library of reference profiles is obtainable by the method of any one of claims 88, 91 or 94.

98. A method of finding an alternative treatment for a human disease which method comprises the steps of:

- (a) exposing an nematode worm to a candidate compound,
- (b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound,
- (c) systematically scoring a plurality of any said changed characteristics to establish a phenotypic profile for said compound, and
- (d) comparing said profile with a library of referenced profiles, wherein said library of referenced profiles is obtainable by carrying out the method in accordance with any one of claims 88, 91 or 94.

09857473 081704

99. A method of finding a biochemical pathway in which a compound known to have pharmacological activity acts which method comprises the steps of:

(a) exposing a nematode worm to the known compound, measuring any changes in the identifiable characteristics of said worm as a result of exposure to said

5 compound,

(b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound,

(c) systematically scoring a plurality of any said changed characteristics to establish a phenotypic profile for said compound, and

10 (d) comparing said profile with a library of reference profiles, said library of reference profiles being obtainable by the method of any one of claims 88, 91 or 94.

100. A method of finding a potential new medicinal indication for a compound of known pharmaceutical activity which method comprises the steps of:

15 (a) exposing a nematode worm to the known compound,

(b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound,

(c) systematically scoring a plurality of any said changed characteristics to establish a phenotypic profile for said compound, and

20 (d) comparing said profile with a library of reference profiles, said library of reference profiles being obtainable by the method of any one of claims 88, 91 or 94.

101. A method of identifying the mechanism of action of any side effects associated with a compound of known pharmaceutical activity which method comprises
25 the steps of:

(a) exposing a nematode worm to the known compound,

(b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound,

30 (c) systematically scoring a plurality of any said changed characteristics to establish a phenotypic profile for said compound, and

(d) comparing said profile with a library of reference profiles, said library of reference profiles being obtainable by the method of any one of claims 88, 91 or 94.

09557479.061701

102. A method of attributing a particular gene to a particular biochemical pathway in *C. elegans* which method comprises the steps of:

(a) exposing a nematode worm to a compound known to operate in a particular biochemical pathway,

5 (b) measuring any changes in the identifiable characteristics of said worm as a result of exposure to said compound,

(c) systemically scoring a plurality of any said changed characteristics to establish a phenotypic profile for said compound, and

10 (d) comparing said profile with a library of reference phenotypic profiles, said library of reference profiles being obtainable by carrying out the method in accordance with any one of claims 88, 91 or 94.

103. A method as claimed in any one of claims 96 to 102 wherein said nematode worm is selected from wild-type *C. elegans*, a mutant *C. elegans* comprising one or more mutations, a *C. elegans* carrying a reporter gene or a transgenic *C. elegans*.
15

104. A method as claimed in claim 103 wherein said transgenic *C. elegans* expresses a human gene.

20 105. A method of establishing a phenotypic profile for a nematode worm which method comprises measuring and scoring at least three, preferably at least six and more preferably at least ten characteristics of said worm which are not exhibited by wild-type worms.

25 106. A method as claimed in claim 105 wherein said characteristics not exhibited by wild-type worms are selected from the list shown in Table 1.

30 107. A method as claimed in claim 105 or claim 106 which comprises measuring and scoring changes in two or more characteristics selected from the group consisting of: viability, life cycle, body shape, movement behaviour, mechanotransduction, pharynx pumping, defecation and fertility.

09557478.081701

108. A method as claimed in any one of claims 105 to 107 wherein said phenotypic profile is established for a nematode worm which is selected from a worm having one or more mutations, a worm which has been exposed to a compound or combination of compounds, a transgenic worm, a worm carrying a reporter gene or a worm which has been exposed to an environmental change.

109. A method as claimed in claim 108 wherein said transgenic worm comprises a human gene.

110. A method as claimed in claim 108 wherein said compound has known pharmacological activity.

111. A method as claimed in claim 108 wherein said compound is known to be active in a particular biochemical pathway.

112. A method as claimed in claim 108 wherein said compound or combination of compounds is from a combinatorial library of compounds.

113. A compound which has potential therapeutic activity in a mammal which has been identified in a method as claimed in any one of claims 71 to 81 or 96 to 104.

114. A library of nematode worms obtainable by a method as claimed in any one of claims 87 to 95.

115. A library as claimed in claim 114 wherein said nematode worm is *C. elegans*.

add B1

09557478.061701